Title: Olfactory-specific inflammation and disease severity in chronic rhinosinusitis
PI: Z. Soler, M.D.
Department of Otolaryngology
Institute: National Institute on Deafness and Other Communication Disorders (NIDCD)
Year: 2013

The full proposal can be viewed in the ORD Proposal Library:
https://academicdepartments.musc.edu/research/ord/proposal-library/access.html

1 Hook
2 Current knowledge
3 Gap in knowledge
4 Critical need
5 Hypothesis
6 Specific objectives
7 Narrowing context
8 Broad goal
9 Outcome
10 Public health-related impact
Chronic rhinosinusitis (CRS) is one of the most common causes of impaired olfaction, including subtypes with and without nasal polyposis (CRSwNP and CRSSNP). Although olfactory dysfunction is highly prevalent in patients with CRS, very little is known about its immunopathology and current clinical staging of CRS often fails to correlate with olfactory dysfunction. As a result, impaired smell is often overlooked clinically and remains one of the most troubling and difficult features of the disease to treat. The overall hypothesis of this proposal is that objective olfactory dysfunction in CRS will correlate with localized, olfactory-specific measures of inflammation and disease severity. This cross-sectional study will perform detailed objective olfactory testing in patients with CRS and relate these findings with refined clinical measures of olfactory-specific disease severity to include the inflammatory cytokine profile of the olfactory cleft, olfactory-specific quality-of-life (QOL), and computed tomography (CT) and endoscopic grading of the olfactory cleft. Prior studies of olfactory dysfunction in CRS have shown few correlations with specific immune or clinical parameters. Investigations of the immune profile have focused upon the presence of inflammatory cells in sinus mucosa, primarily eosinophils, using semi-quantitative techniques such as immunohistochemistry. CT and endoscopic measures of CRS have also been poor predictors of olfactory dysfunction, again, likely because they focus upon measuring severity of inflammation in the paranasal sinuses with no attention paid to the olfactory cleft. Similarly, the most commonly utilized CRS-specific QOL instruments include few if any questions related to olfaction. Thus, it is not surprising that these relatively broad measures of CRS disease severity fail to predict olfactory dysfunction. The overarching focus of this proposal is to identify clinically-relevant, olfactory-specific measures of disease severity which correlate with objective olfactory dysfunction. Elucidation of these factors will give insight into mechanisms of disease and will allow physicians to better predict which CRS patients will be affected by olfactory dysfunction and subsequently provide prognostic information regarding therapeutic response.

**AIM 1: To determine whether local cytokine profiles correlate with objective olfactory function in patients with CRS.**

**Rationale:** Olfactory dysfunction is a product of ongoing mucosal inflammation and the immune dysregulation characterizing subtypes of CRS. Few studies have directly examined inflammation of the olfactory cleft due to the risk and inherent difficulty of obtaining mucosal biopsies of this region and instead have used semi-quantitative techniques to measure inflammation in the adjacent paranasal sinuses. These studies have found limited correlation between sinus inflammation and olfactory dysfunction. Methods: Olfactory threshold, discrimination, and identification will be assessed using commercially available Sniffin’ Sticks testing kits (Burghardt, Wedel, Germany). Pro-inflammatory mucus cytokines will be sampled via targeted sponge placement during sinonasal endoscopy and assayed by cytometric bead array and enzyme-linked immunosorbent assay (ELISA). Correlation between objective olfactory function and the secretory cytokine profile of the olfactory cleft will be examined.

**Hypothesis:** Specific pro-inflammatory cytokines will correlate with objective olfactory testing and this profile will differ between CRS subtypes. We expect CRSwNP to display a more Th2-skewed profile, CRSSNP a mixed Th1/Th2 profile, and there to be some overlap of involved cytokines between subgroups.

**AIM 2: To determine whether olfactory-specific disease severity measures correlate with objective olfactory function and compare this to existing CRS-specific measures.**

**Rationale:** Common CRS-specific clinical measures, including QOL scores (SinoNasal Outcome Test 22; SNOT-22), CT (Lund-Mackay), and sinonasal endoscopy (Lund-Kennedy) fail to correlate with olfactory dysfunction. This is likely due to their general nature which focuses upon the paranasal sinuses rather than examining the olfactory cleft and subjective olfaction.

**Methods:** Olfactory threshold, discrimination, and identification will be assessed using Sniffin’ Sticks testing kits. Correlation between objective olfactory function and clinical measures of olfactory-specific disease severity will be determined, including olfaction-specific QOL (Questionnaire for Olfactory Dysfunction; QOD) and refined CT and endoscopic measures which focus upon the olfactory cleft.

**Hypothesis:** Olfactory-specific disease severity measures will correlate with objective olfactory function more robustly than broad, non-specific measures for both CRSwNP and CRSSNP subtypes.

**Relevance and Future Directions:** Findings from this study will provide important preliminary data for a planned R01 submission which will longitudinally examine those factors, clinical and immunologic, which impact olfaction and predict response to medical and surgical treatment. This data will lay the groundwork for future mechanistic studies of olfactory dysfunction to determine the cellular sources and specific pathways for key olfactory-related cytokines and determine whether targeted reduction results in improved olfaction.